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FUNCTIONAL MAGNETIC RESONANCE IMAGING SHOWS POTENTIAL FOR PREDICTING INDIVIDUAL DIFFERENCES IN FATIGUE VULNERABILITY

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This report has been reviewed and is approved for publication.

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14. ABSTRACT
Fatigue from sleep loss exerts deleterious effects on group performance, and some individuals are more affected than others. Underlying patterns of cortical activation may partially account for such individual differences. The present research utilized fMRI procedures to examine the non-sleep-deprived cortical activation of a group of active-duty military pilots on whom the effects of sleep loss had previously been quantified. The pilots completed a Sternberg Working Memory Task (SWMT) alternately with a control task during 13-minute scans. Examination of the number of activated voxels in response to SWMT indicated that, as a group, the pilots were more similar to a group of fatigue-resistant non-pilots than to a group of fatigue vulnerable non-pilots. In addition, within the pilot group, the number of activated voxels was significantly related to the level of fatigue vulnerability on a simulator flight-performance task. Thus, it appears that baseline fMRI scans may be useful for predicting fatigue susceptibility.

15. SUBJECT TERMS
Fatigue, Sustained Operations, Modafinil, Provigil, Aviation, Fighter pilots, Countermeasures

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BACKGROUND

In general terms, fatigue and sleepiness from inadequate sleep are associated with decrements in performance (Caldwell et al., 2003; Dement and Vaughan, 1999; Dinges, 1995; Van Dongen, Maislin, Mullington, and Dinges, 2003), increased safety risks (Leger, 1994; Mitler et al., 1988; Webb, 1995), and adverse health consequences (Briones et al., 1996; Buysse and Ganguli, 2002). However, pilot fatigue is particularly problematic in both civil and military aviation. This is because so many flight operations involve sleep loss from circadian disruptions, extended work periods, and night duty, and all of these factors can severely compromise aircrew alertness (Akerstedt, 1995a; Akerstedt, 1995b). In the worst cases, pilots can fall asleep at the controls (Caldwell and Gilreath, 2002; Co, Gregory, Johnson, and Rosekind, 1999; Rosekind, Co, Gregory, and Miller, 2000). More often however, fatigued aircrews remain awake, but experience compromised motivation, precision, and attention (Perry, 1974). In addition, overly-tired aviators experience general reductions in central nervous system (CNS) activation that can seriously impair performance. In-flight studies have shown that pilot fatigue can precipitate EEG "micro-events" that are indicative of brief episodes of involuntary sleep in the cockpit (Rosekind et al., 1994; Samel et al., 1997; Wright and McGown, 2001). Flight-simulation studies also have documented sleepiness-related increases in slow-wave brain activity in military (Caldwell et al., 2003) and commercial pilots (Neri et al., 2002). Such EEG findings are particularly disconcerting because there is evidence that this type of brain activity often mirrors degradations in flight skills (Caldwell et al., 2003), neurobehavioral performance (Cajochen, Khalso, Wyatt, Czeisler, and Dijk, 1999), attention and vigilance (Makeig and Jung, 1995; 1996), and reaction time (Lorenzo, Ramos, Arce, Guevara, and Corsi-Cabrera, 1995).

The impact of fatigue on aviation safety

Needless to say, fatigue from inadequate sleep is an aviation safety hazard. In fact, an NTSB study of major accidents in domestic air carriers from 1978 through 1990 in part concluded that crew sleepiness was related to increased procedural and tactical decision errors on the flight deck (NTSB, 1994, p. 75). Kirsh (1996) estimates that fatigue may be involved in 4-7% of civil aviation mishaps, and data from the U.S. Army suggest fatigue is involved in 4% of all Army aviation accidents (Caldwell and Gilreath, 2002). Luna (2003) reported that fatigue has played a role in 7.8 percent of the Air Force's total reportable Class A mishaps from 1972 to the year 2000.

The importance of individual differences

On average, it has been estimated that every 24 hours without sleep leads to performance declines of approximately 25-30 percent (Angus and Heslegrave, 1985; Belenky et al., 1994). However, recent reports make it clear that what is known about the *average* response to sleep loss obscures the fact that there are wide variations in *individual* responses to fatigue (Balkin et al., 2000; Van Dongen, Rogers, and Dinges, 2003). Unfortunately, little is presently known about the magnitude of these between individual variations in fatigue susceptibility and the factors that underlie individual differences in fatigue vulnerability.

Although vast differences in the more general characteristics of individuals have long been recognized (Tyler, 1965), Wilkinson (1974) was evidently the first to make note of the fact that average group responses to stressors, such as sleep deprivation, do not accurately convey the impact of these stressors across different individuals. Since the time of Wilkinson (1974), few other scientists have focused research on variations in individual responses to sleep loss. However, Morgan, Winne, and Dugan (1980) have

substantiated the presence of individual differences in the responses to acute sleep deprivation (44 hours of continuous wakefulness). In this study, the synthetic-work performance of some subjects was degraded by as much as 40 percent while the performance of others was essentially unaffected. Balkin et al. (2000) reported that systematic sleep restriction (chronic sleep deprivation) also produced differential amounts of degradations in different subjects. Such divergent effects were observed on basic vigilance tasks as well as driving simulations. Belenky et al. (2001) found differences in susceptibility in fatigue produced by 7 days of sleep restriction (3 hours of sleep every 24 hours) on a psychomotor vigilance. Caldwell et al. (2003) showed that even well-trained, fully-experienced, military fighter pilots were not uniformly affected by fatigue. Although the flight-simulator performance of the group declined an average of 52 percent as a result of 26-37 hours of sleep deprivation, individual impairments ranged from 135 percent in one case to only 0.6 percent in another.

Factors responsible for differences in fatigue tolerance

The factors underlying such differences in fatigue vulnerability have yet to be determined, but Mallis et al. (2001) and Van Dongen, Baynard, Nosker, and Dinges (2002) have indicated that whatever accounts for individual differences in the responsiveness to fatigue is a relatively stable, trait-like characteristic. In other words, an individual who is fatigue resistant on one occasion likely will be fatigue resistant on others and vice versa. Van Dongen et al. (2002) found that subjects who were exposed to two 36-hour sleep-deprivation periods were similarly affected on both occasions even though the periods were separated by 2-4 week intervals. Morgan et al. (1980) likewise found that subjects who were subjected to 4 different 44-hour periods of sleep deprivation responded consistently on each occasion despite the fact that each sleep-loss

period was separated by a one week interval. Thus, fatigue tolerance/vulnerability seems to be a relatively stable individual trait. But it remains to be determined whether this trait can be predicted and used for practical purposes such as to select people who are particularly well-suited to fatigue-inducing jobs.

The role of subject characteristics

There is limited evidence that the vulnerability to sleep loss may be related to overtly-observable characteristics such as personality makeup, age, or measurable sleep needs, and such associations might help to identify fatigue-resistant individuals. For instance, there is evidence that neurotic extroverts are more affected by sleep loss than non neurotic extroverts (Blagrove and Akehurst, 2001); younger people are somewhat less tolerant to sleep deprivation than their older counterparts (Belenky, Bliese, Wesenten, and Balkin, 2003); and subjects who have greater sleep needs are often less fatigue resistant than those with lesser sleep needs (Blagrove, 2001; Van Dongen, Roger, and Dinges, 2003). However, none of these characteristics are an accurate "litmus test" for the presence or absence of fatigue susceptibility, and for this reason, other possibilities, such as potential physiological markers, are being explored.

Underlying neuro-physiological contributors

The EEG often has been used in an attempt to explain the changes in behavioral performance capacity known to occur during periods of sleep deprivation (Pigeau, Heslegrave, and Angus, 1987; Lorenzo et al., 1995; Smith, Envoy, and Gevins, 2002), but no published documentation was found of successful efforts that used pre-sleep-deprived EEG evaluations to predict individual susceptibility to sleep loss. In fact, even though low-frequency EEG activity has been used as a marker for the increased homeostatic sleep pressure that often adversely affects behavioral performance

(Cajochen, Brunner, Krauchi, Graw, and Wirz-Justice, 1995; Cajochen et al., 1999), such data do not accurately predict individual susceptibility to fatigue. In fact, Aeschbach et al. (2001) found that while the kinetics of the homeostatic sleep drive (as measured via EEG) were similar in short sleepers and long sleepers, short sleepers were simply better able to tolerate higher homeostatic pressure than their longer-sleeping cohorts. Thus, sleep needs alone (and by inference, electrophysiological measures of sleep pressure) are not sufficient to account for the trait-like inter-individual differences in how individuals will respond to sleep loss (Van Dongen, Rogers, and Dinges, 2003).

Advanced neuro-imaging studies

Perhaps the underlying determinants of fatigue vulnerability will be found in more advanced explorations of the types of brain imaging studies that have begun to more precisely characterize the effects of sleep deprivation on global and regional CNS changes using Positron Emission Tomography (PET) (Thomas et al.. 2000) and blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) (Allen, 2000; Drummond and Brown, 2001; Mu et al., submitted). In fact, recent work by Mu et al. (in press) indicated that individual differences in fatigue vulnerability may be related to trait-like differences in global CNS activation that are detectable prior to an episode of sleep loss. After conducting baseline fMRI scans on subjects who were alternately performing a Sternberg Working Memory Task (SWMT) and a control task in the scanner, Mu et al. (in press) discovered that the fatigue-resistant subjects had more global cortical activation (number of activated voxels) even in the non-sleep-deprived state than the fatigue-vulnerable subjects. This suggested an association between fatigue vulnerability and baseline brain activity that could be exploited in a selection context.

OBJECTIVES

The current research sought to determine whether baseline fMRI data could be used to predict fatigue susceptibility in a group of volunteers known to commonly encounter job-related sleep loss. To accomplish this objective, performance data from a group of military pilots who had recently undergone sleep-deprivation testing during 37-hour periods of continuous wakefulness (Caldwell et al., 2003) were merged with non-sleep-deprived fMRI data collected from these same pilots approximately 3-6 months after the period of sleep deprivation. The two data sets were examined for the presence of statistically-significant correlations. Following from the Mu et al. (in press) study, we hypothesized that the baseline BOLD fMRI activation during the Sternberg Working Memory Task would vary as a function of sleep deprivation vulnerability, with more resilient individuals having more baseline activation. This study was thus an attempt to test and extend the earlier work (Mu et al., in press).

METHODS

This research consisted of three phases. During the first phase, the simulator flight performance of 10 active-duty Air Force pilots was evaluated during 37 hours of continuous wakefulness. Testing was performed in an operational F-117 simulator-testing environment at Holloman AFB, NM. This phase quantified the impact of fatigue on piloting skills and characterized the extent of individual differences in fatigue vulnerability. During the second phase, 8 of these 10 pilots traveled to the Medical University of South Carolina to participate in fMRI evaluations conducted under non-sleep-deprived conditions. This phase provided information about how the pilots' baseline cortical activation compared to the cortical activation of the fatigue-resistant versus fatigue-vulnerable non-pilots that were earlier assessed in the Mu et al. (in press) study. During the third phase of the research, the

fMRI data on the pilots were combined with the earlier-obtained flight-performance data, and correlational analyses were performed. This phase yielded information about the degree to which individual differences in fatigue vulnerability could be predicted by fMRI-derived differences in brain activation.

Subjects

There were 10 F-117 fighter pilots who participated in the first phase of the study. The average age of this group was 35.7 yrs (range: 27-43 years). The participants were enrolled after signing an informed consent agreement (approved by the Air Force Institutional Research Board) and after passing a medical prescreen. For the second phase of the research, 8 of these 10 participants (mean age, 35.9; range, 30-43 yrs) agreed to participate in the fMRI imaging which was conducted at the Medical University of South Carolina (MUSC). These volunteers were enrolled after signing additional informed consent agreements (approved by the Air Force Institutional Review Board and the MUSC Institutional Review Board). In the third phase of the research, one of these eight pilots was excluded from the correlational data analysis due to the fact that his performance (from the flight-simulator phase of the research) was found to be two standard-deviations below the performance of the group as a whole, and this raised concerns about the motivational level of this particular individual. The mean age of the participants who made up the correlational data set was 36.1 years (range: 30-43 years).

All of the pilots were in good health as evidenced by the fact that they all possessed recent flight physicals (F-117 pilots are required to pass physical examinations every 6 months in order to maintain their flight status). None were taking any type of medication known to impact mental alertness. In addition, none of the pilots was working a non-standard work schedule during any phase of the research. Thus, circadian

factors would not have confounded their responses to sleep deprivation (in the first phase) or the validity of their fMRI data (in the second phase). As a group, the 7 pilots who made it into the third phase of the research reported an average of 7.7 (SD = .517) hours of sleep prior to the flight-simulation testing at Holloman AFB and 6.7 (SD = 1.011) hours of sleep prior the fMRIs at MUSC. Their reported habitual sleep averaged 7.8 (SD = .424) hours per night.

No data were collected on habitual caffeine consumption. Although caffeine use was restricted during the first phase of the research (the flight simulation phase) no such restrictions on caffeine or other characteristic preferences or behaviors were instated during the second phase of the research (the fMRIs).

Apparatus

Flight simulator testing

The first phase of the research was conducted at Holloman Air Force Base, NM using the F-117 Weapon Systems Trainer (WST) that was typically used as a training device and as one method for sustaining pilot proficiency in the actual F-117 aircraft. The WST (L3 Communications/Link Training and Simulation) is a stationary digital device that simulates the characteristics and operations of the F-117A stealth fighter aircraft currently in the U.S. Air Force inventory. It provides a fully-functioning replica of the interior cockpit of the actual aircraft, including all primary and secondary flight controls, aural cues (engine sounds), and cockpit lighting (L-3 Communications, 1993). The components of the WST include the simulator itself as well as an instructor/operator station (IOS), a computer complex that includes an Alpha Server 8200 (Digital Equipment Corp.) and Input/Ouput (I/O) cabinets, and the equipment necessary for the generation of out-of-the-window visual scenes. Objective flight performance data were collected using the Coherent Automated

Simulation Test Environment (CoASTE) tool—a set of software routines that normally provide the capability to evaluate simulator performance, display/manipulate various data from simulator data pools, and/or trace and correct problems. The CoASTE's trace utility was used to capture various parameters of flight performance data at a rate of 2 Hz throughout each flight.

Neuro-imaging

The second phase of the research was conducted at the MUSC Imaging Center, Charleston, SC. All images were acquired with a 3T MRI scanner (Intera, Philips Medical System) using a send/receive single channel head coil. A set of T_1-weighted axial structural images encompassing the whole brain was acquired using the following parameters: TR = 625 ms, TE = 20 ms, slice thickness = 5 mm, interslice gap = 1 mm, field of view (FOV) = 25.6 cm, number of slices = 24, matrix = 256 x 256. With the same slice coverage as with the structural scans, a whole brain gradient echoplanar imaging (EPI) sequence was employed to acquire continuously on 24 slices in an ascending fashion in axial plane for each functional scan, the parameters used were TR = 2670 ms, TE = 40 ms, FOV = 25.6 cm, image matrix = 64 x 64, in-plane pixel size = 4 x 4 mm^2, slice thickness = 5 mm, interslice gap = 1 mm. 160 1-mm contiguous axial high-resolution anatomical images were also acquired for each subject (256 x 256 matrix, FOV = 25.6 cm). Functional analyses were conducted with Statistical Parametric Mapping software (SPM 2, Wellcome Department of Cognitive Neurology, London, UK).

Correlational analyses

The third phase of the research did not involve additional subject testing, but rather involved the merging and further analysis of data that had already been collected. The fMRI data analysis was performed at MUSC, where no personnel knew of the

prior sleep deprivation results. These blinded data were then shipped to the Air Force Research Laboratory, Brooks City-Base, TX.

Procedure

Flight simulation testing

The first phase of the research was designed primarily to assess the impact of fatigue associated with 37 hours of continuous wakefulness on basic piloting skills. Secondarily, the study sought to examine the range of individual differences in susceptibility to fatigue in a group of well-trained, experienced pilots who are often required to work long hours on non-standard schedules. The simulator flights in this phase of the research (at Holloman AFB, NM) were set up for night illumination conditions with zero visibility and no visible lighting on the horizon. In addition, the WST was programmed to generate zero air turbulence with no wind gusts in order to prevent non-pilot-related flight-path deviations. The auto-throttle and auto-pilot modes (which can automatically maintain designated flight paths) were disengaged to force all participants to "hand fly" the simulator. Flight performance was monitored by a computer system which sampled headings, altitudes, airspeeds, bank angles, and vertical-velocities at a rate of 2 Hz throughout each flight.

General procedures. This "fatigue-susceptibility" phase of the research involved a 3-day time commitment from each participant. During this phase, there were few restrictions on the participants' activities and schedules on the first day (a training day), but more structure was imposed on the second day (this was the beginning of the sleep-deprivation period). For day 2, the pilots were instructed to awaken at 0700 after obtaining approximately 8 hours of sleep. They also were instructed to refrain from napping between the wake-up time and the time at which they reported for testing.

Compliance with both of these instructions was facilitated by requiring the pilots to wear wrist activity monitors. The data from these monitors also offered an objective estimate of sleep duration times which could later be factored into the data analysis. Participants were asked to refrain from caffeine consumption after 1000 in the morning on day 2 (the first day of the sleep-deprivation period), and for the remainder of the testing period (during the last 34 hours of continuous wakefulness).

Schedule. The schedule was as follows: On the first day, there were 3 training/familiarity sessions, and over the next 2 days, there were 5 testing sessions that covered the final 23 hrs of the sleep-deprivation period. Training flights were conducted at 1400, 1700, and 2000 on day 1. Testing flights were conducted at 2300 on day 2, and at 0400, 0900, 1400, and 1900 on day 3.

Flight testing. During each flight, participants completed 13 standardized maneuvers (2 right 360° turns, a left 360° turn, 5 straight-and-level segments, a climb and a descent, a right-descending and left-climbing turn, and a 720° left turn) to assess the impact of fatigue on basic flight skills. The pilots were instructed when to begin each of the flight maneuvers by a console operator seated outside of the simulator. This console operator ensured that the correct flight parameters were being maintained before each maneuver was started, but no performance feedback was provided during the individual maneuvers. The exact same flight profile was flown on each of the three training sessions and each of the five testing sessions. In between the flights, participants were given rest breaks or administered other tests (see Caldwell et al., 2003). They were released from the test facility following the 1900 flight on day 3.

Data analysis. Analysis of the flight performance data (performed on the data derived from all 10 of the participants) began by converting the raw flight data into root-

mean-square errors (RMS errors) to objectively quantify deviations from assigned flight paths. Next, the RMS-error data were converted into scores that represented the "percentage change from baseline," with the last training session used as baseline. The following formula was used which allows decreases in performance to be represented by negative percent changes:

Percent Change = ((Baseline - Score)/Baseline) x 100.00.

These data were analyzed with BMDP4V, Repeated Measures Analysis of Variance (ANOVA) for time (2300, 0400, 0900, 1400, and 1700) and maneuver (right turn, left turn, climb, descent, left-climbing turn, right-descending turn, left-720-degree turn, and straight-and-level). Follow-up tests on the time main effect consisted of regression evaluations for the presence of linear, quadratic, and cubic trends (also calculated with BMDP4V). The maneuver main effect was not explored for the purposes of this report.

Neuro-imaging

The second phase of the testing was designed to determine whether individual differences in fatigue susceptibility (noted from the first phase of the research) might be associated with differences in CNS activation that could be detected in the non-sleep-deprived brains of the pilots. For this part of the research, the fMRI data from the pilots were compared to fMRI data from fatigue-vulnerable and fatigue-resistant non-pilots. The fMRIs conducted during this part of the research were performed at MUSC approximately 3-6 months after the pilots had completed the flight-performance evaluations discussed above. Eight of the 10 pilots agreed to participate in this second phase of testing. Five of the pilots were imaged in the morning, and three of the pilots were imaged in the afternoon (all on Thursdays).

General procedures. Each of the pilots spent approximately 2 hours at the imaging center during which time they completed a questionnaire regarding their previous night's sleep and their usual (habitual) amount of sleep, a Visual Analog Scale (VAS) which described their current level of sleepiness, and an Epworth Sleepiness Scale which described their usual level of sleepiness. Following the collection of these data, each pilot completed an fMRI evaluation.

fMRI and Sternberg testing procedures. While undergoing the fMRI scan, participants performed the Sternberg Working Memory Task (SWMT). Although they were not trained to asymptotic performance levels on the SWMT due to time constraints, they were familiarized with the test procedures prior to the scan. Briefly, each functional scan consisted of 12 blocks. Each block included a control task (32 s) with an alternative Sternberg task (32 s), starting from the control task. Each task contained two trials. The whole functional scan lasted 12 min. 48 s. An Integrated Functional Imaging System (IFIS) (Gainesville, FL) was used to display the letters and asterisks that allowed subjects to view the stimuli on an LCD screen in front of their eyes. Each subject was required to use a response button to respond "Yes" or "No" following a visual prompt, where the 'yes' or 'no' response was either on the left or right side. Subjects were instructed to hold a button box with their hands and depress the left thumb for the left button and the right thumb for the right button. Subjects were instructed to keep their heads still for the entire scan. The control task consisted of quickly viewing 6 asterisks in 2 rows, and then after a 7-s delay, viewing a word "YES" or "NO" presented at the center of the screen. During the control task, each subject was asked to simply follow the response of "Yes" and "No" when "YES" or "NO" was presented on the IFIS screen; the order of "YES" and "NO" was at random. During the Sternberg task, one of three types of letter tasks, namely one

letter, three letters, and six letters, was randomized to display on IFIS screen as source letters. Subjects viewed a set of letters for 3 seconds (2 rows of each consisted of up to 3 letters (1, 3, or 6) or asterisks). They then maintained this set in mind across a short time delay (7-s), and then indicated whether a probe letter corresponded to one of the letters in the immediately previous set. Reaction times and error rates were recorded within the IFIS.

fMRI data generation. Functional analyses were conducted with Statistical Parametric Mapping software. EPI scans were corrected for motion and coregistered to the T_1-weighted structural images. After motion correction, all functional scans had residual motion movement less than 1 mm in any of the three planes and were thus included for further analysis. The functional images were then spatially normalized to SPM template and resampled with a voxel size of $2 \times 2 \times 2\,mm^3$ (Ashburner, 1999). After normalization, functional images were spatially smoothed using a Gaussian kernel with 6 mm full width at half maximum (FWHM) to condition for random field theory which was applied to correct for multiple comparisons in statistical parametric mapping (Worsley, 1995). For creating individual t-maps, the block design was convolved with a hemodynamic response function that approximated the activation patterns. Effects at each and every voxel were estimated using the general linear model at the first statistical level. A box-car reference function modeled the activation blocks. The motion-recorded parameters generated during the "realign" process were applied to reject the motion-related activation as six user-specified regressors. A high pass filter (cut off frequency = 128 s) was used to remove possible effects of low-frequency changes. The activated and deactivated t-maps were generated by defining the contrast -1 1 0 0 0 0 0 0 and 1 -1 0 0 0 0 0 0, where -1, 1 represented the contrast of Sternberg task vs. control task, 1 -1

represented the contrast of control task vs. Sternberg task, and 0 indicated that the activation or deactivation associated with the motion-movement would be rejected. Voxel values for the contrasts of interest yielded a statistical parametric map of the t statistic (SPM T), subsequently transformed to the unit normal distribution (SPM Z).

Eight individual contrast images generated at the first statistical level were used to create a group t-map in a random-effects model (Friston and Frackowiak, 1997); cluster analyses were performed and the group t-map was thresholded at dynamic significant levels from $p < 0.05$ to $p < 0.0001$ with a spatial extent of $p < 0.05$, corrected for multiple comparisons (Friston et al, 1994). This procedure yielded the global number of activated voxels as well as the number of activated voxels in the prefrontal and parietal regions.

Data analysis. At the identical threshold $p < 0.01$ with a spatial extent of $p < 0.05$, (corrected for multiple comparisons), data analysis in this phase of the research consisted of comparing the global number of activated voxels from the group map of the eight pilots who agreed to be imaged to the global number of activated voxels from the two groups of non-pilots who had been evaluated during a previous investigation at MUSC. This was accomplished with a one-way, between-groups ANOVA (using BMDP 4V). A significant overall group effect was further examined using pairwise contrasts.

Correlations between flight data and fMRI data

The next phase of the research involved merging the fMRI data from the 8 pilots who were imaged (excluding the one who was found to be a 2 standard-deviation outlier in terms of simulator flight performance) with the flight performance data collected 3-6 months earlier at Holloman AFB. Seven participants were included in this analysis. The fMRI data included the global number of activated voxels (from individual t-maps) as well as the activated voxels in the left-prefrontal, right-prefrontal, left-parietal, and right-parietal

areas. In addition, information about the amount of sleep prior to the flight simulation testing (based on actigraphy data), self-reported habitual nightly sleep, self-reported pilot flight experience (hours of flight time), and the individual ages of each of the pilots was examined (correlated with the flight-performance data) to determine whether these could have confounded correlations between the fMRI results and the performance results. Pearson product-moment correlational analyses were conducted using BMDP AM, Detailed Data Description and Estimation, and BMDP 6D, Bivariate Scatter Plots.

RESULTS

Effects of continuous wakefulness on flight performance (Phase 1)

As noted above, the simulator flight performance (measured 5 times during the final 23 hours of a 37-hour period of continuous wakefulness) was evaluated to determine the effects of fatigue on the group as a whole and on the individuals within the group.

The overall group effect

The two-way ANOVA that examined the impact of both testing time and flight maneuver on basic piloting skill revealed a time main effect ($F(2.44,21.93)=10.72$, $p=.0003$) which was a function of significant linear ($p<.05$), quadratic ($p<.05$), and cubic ($p=.05$) trends in the data. As can be seen in Figure 1, group flight performance degraded from 2300 to 0900, remained consistently poor from 0900 to 1400, and then recovered slightly (although not to pre-deprivation levels) at 1900. In addition to these effects, there was an overall difference among the individual maneuvers ($F(4.79,43.10)=3.83$, $p=.0064$), but this finding was not considered worthy of follow-up since it is well known that some maneuvers are more difficult to perform than others. There was no time-by-maneuver interaction, indicating that none of the maneuvers was more sensitive to the effects of fatigue than the others.

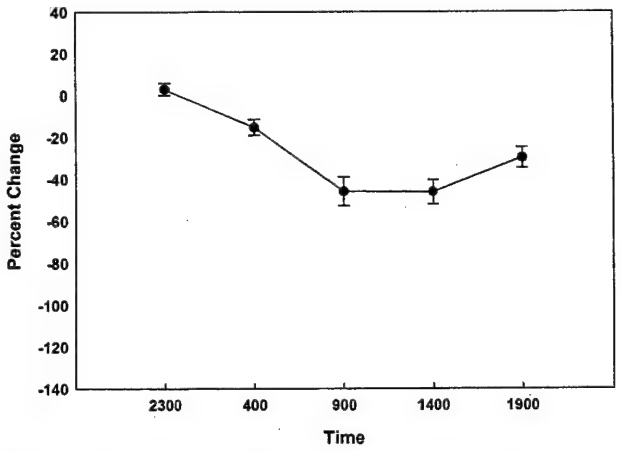

Figure 1. The overall group effects of continuous wakefulness on the accuracy with which the flight maneuvers were performed.

The extent of individual differences

There is no universally-agreed upon method for analyzing the magnitude of individual differences in the presence of a statistically significant group effect. However, the data were visually inspected in an effort to gauge the extent of individual differences in the present research. Figure 2 shows that one of the pilots was largely unaffected by the sleep loss imposed in this investigation, whereas another was degraded by a full 135 percent. Although this "most affected" pilot was later excluded from the correlational analyses between flight performance and fMRI data (for reasons described earlier), large individual differences nevertheless remained.

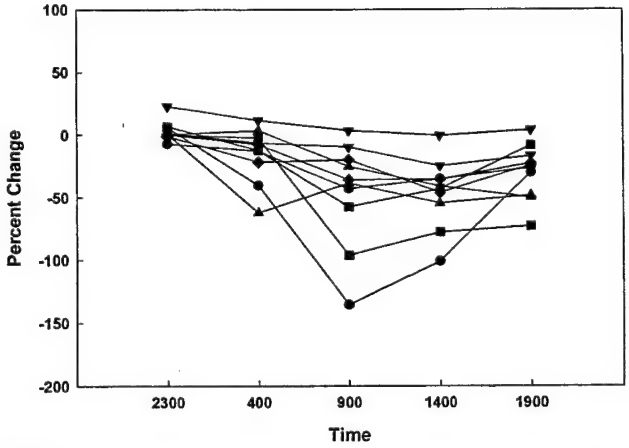

Figure 2. Individual variability in the effects of continuous wakefulness on the accuracy with which the flight maneuvers were performed.

Similarities between the pilots and the non-pilots (Phase 2)

Eight of the pilots who were evaluated in the continuous-wakefulness study subsequently agreed to participate in the fMRI component of this research. Upon completion of the imaging, the global activation data from these individuals, using the group t-maps, was statistically compared to the global activation data collected from non-pilots who were earlier classified as "fatigue resistant" and non-pilots who were earlier classified as "fatigue vulnerable" (Mu et al., in press). The results of the one-way, between-groups ANOVA indicated that there was a statistically-significant difference among the groups ($F(2,25)=36.2$, $p<.0001$). Subsequent pairwise contrasts revealed that this overall effect was attributable to the fact that all of the groups differed from one another ($p<.01$). As shown in Figure 3, the pilots were characterized by the greatest amount of global activation, the fatigue-resistant non-pilots were next, and the fatigue-vulnerable non-pilots evidenced the least amount of global activation. The group fMRI maps are shown in Figure 4.

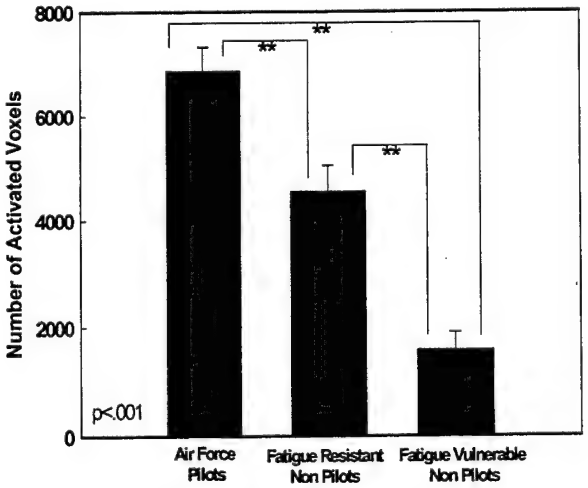

Figure 3. The global number of activated voxels, based on group t-maps, in the pilot group was more similar to what was observed in fatigue-resistant non-pilots than in fatigue-vulnerable non-pilots.

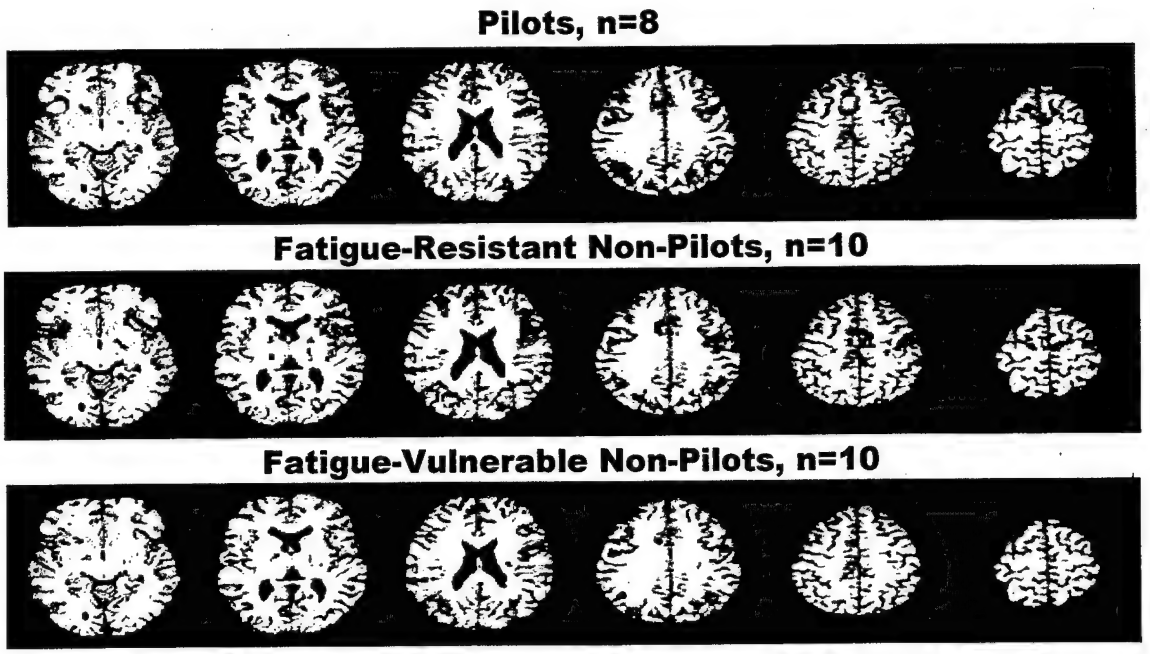

Figure 4. Average T-maps of the pilots, the fatigue-resistant non-pilots, and the fatigue-vulnerable non-pilots during performance of Sternberg Working Memory Test (SWMT) in the MRI scanner. (Maps were thresholded at $P < 0.01$ with a spatial extent $P < 0.05$, corrected for multiple comparisons.)

Relationship between fMRI data and fatigue vulnerability (Phase 3)

Once the eight pilots were imaged at MUSC, data on global and regional activation, from individual t-maps, was correlated with data showing the *average flight-performance decrement* and the *maximum flight-performance degradation* recorded earlier from the continuous wakefulness study. In Table 1, the data for all eight pilots have been ranked, based on the average flight-performance decrement, from most fatigue-resistant to least fatigue-resistant. As noted earlier, one of the eight pilots who agreed to be imaged in the fMRI phase was excluded from this analysis because his maximum flight-performance decrement identified him as being a two-standard-deviation outlier. This excluded subject is the last one listed in the table.

Table 1. Merged data from the simulator study and the fMRI evaluations

Age	Total flight time	F-117 flight time	Sleep prior to sim. study (h.mm)	Reported sleep prior to fMRI (h.mm)	Self-reported usual sleep (h.mm)	Avg flight-perf. decrement	Max flight-perf. decrement	Global number Active voxels	Left Pre-frontal number active voxels	Left Parietal number active voxels	Right Pre-Frontal number Active voxels	Right Parietal number Active voxels
30	929.0	52.9	8.00	5.3	8	8.213	-0.613	59757	9825	7385	10196	6992
43	3028.8	42.4	8.30	6.45	8	-11.370	-25.038	51342	12095	8526	9287	3941
37	2937.3	1034.9	8.20	6	7	-22.623	-50.075	33335	10806	5827	5876	2919
28	970.0	48.1	7.05	7	8	-22.726	-46.388	45287	12627	4434	7722	3047
43	4394.7	828.8	7.10	8	8	-22.985	-57.475	43756	9607	5258	6700	3124
42	2781.7	991.4	7.38	8	7.3	-24.950	-43.050	25363	6770	4222	3826	2232
30	1300.9	287.8	7.50	6.3	8	-40.610	-62.125	28256	6348	4576	3647	2704
34	1676.7	491.0	6.30	5.3	6	-60.105	-135.200	39472	10737	5572	6463	3602

Correlations with average flight performance

The bivariate correlations conducted on the data from the remaining seven pilots revealed a statistically-significant relationship between average flight performance and the global number of activated voxels, based on the individual t-maps, ($r=0.849$, $p=.016$); between the average flight performance and the activated voxels in the right prefrontal region ($r=0.872$, $p=.011$); and between the average flight performance and the activated voxels in the right parietal region ($r=0.899$, $p=.006$). The correlation between average flight performance and the activated voxels in the left parietal region was marginally significant ($r=0.727$, $p=.064$). There was not a strong association between the average flight performance and the activated voxels in the left prefrontal region.

The pattern of results in terms of global activation is shown in Figure 5. The bivariate scatter plots for the regional data are depicted in Figure 6. Note that with the exception of the left-prefrontal data, pilots with the most CNS activation during the SWMT in the non-sleep-deprived state showed the greatest resistance to fatigue-related performance decrements during a period of sleep deprivation (assessed in terms of average deviation from baseline across all five flights). This pattern of results also can be seen in the fMRI maps for each of the seven pilots. In Figure 7, these maps have been

arranged in rank order so that the least-affected pilot appears at the top, and the most affected pilot appears at the bottom.

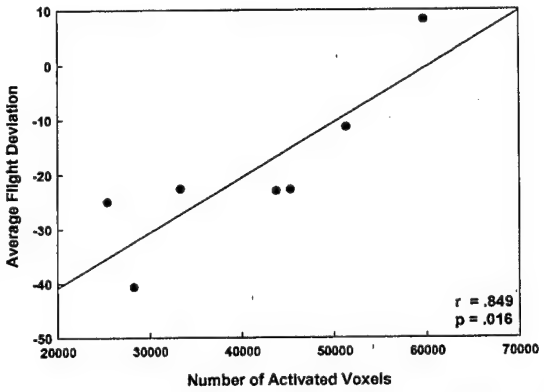

Figure 5. The correlation between the number of activated voxels (global, based on individual t-maps) and the average flight-performance accuracy during sleep deprivation.

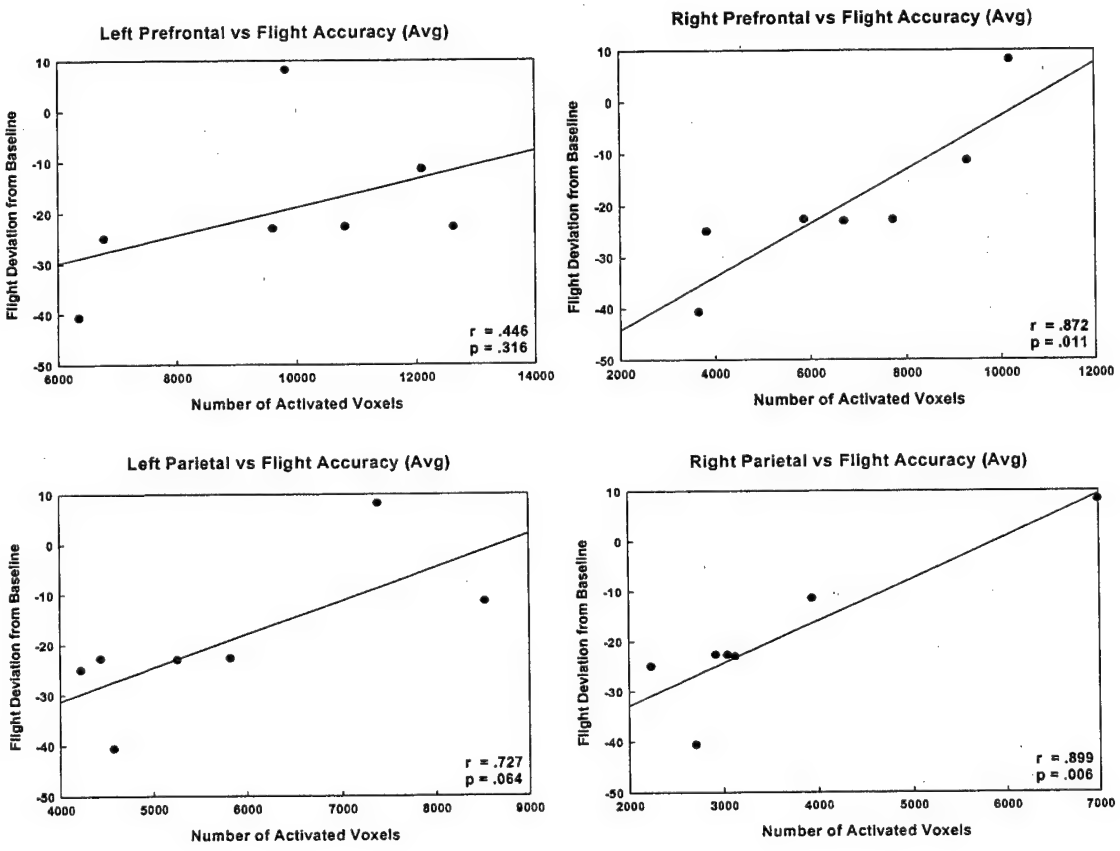

Figure 6. The correlation between the number of activated voxels (regional) and the average flight-performance accuracy during sleep deprivation.

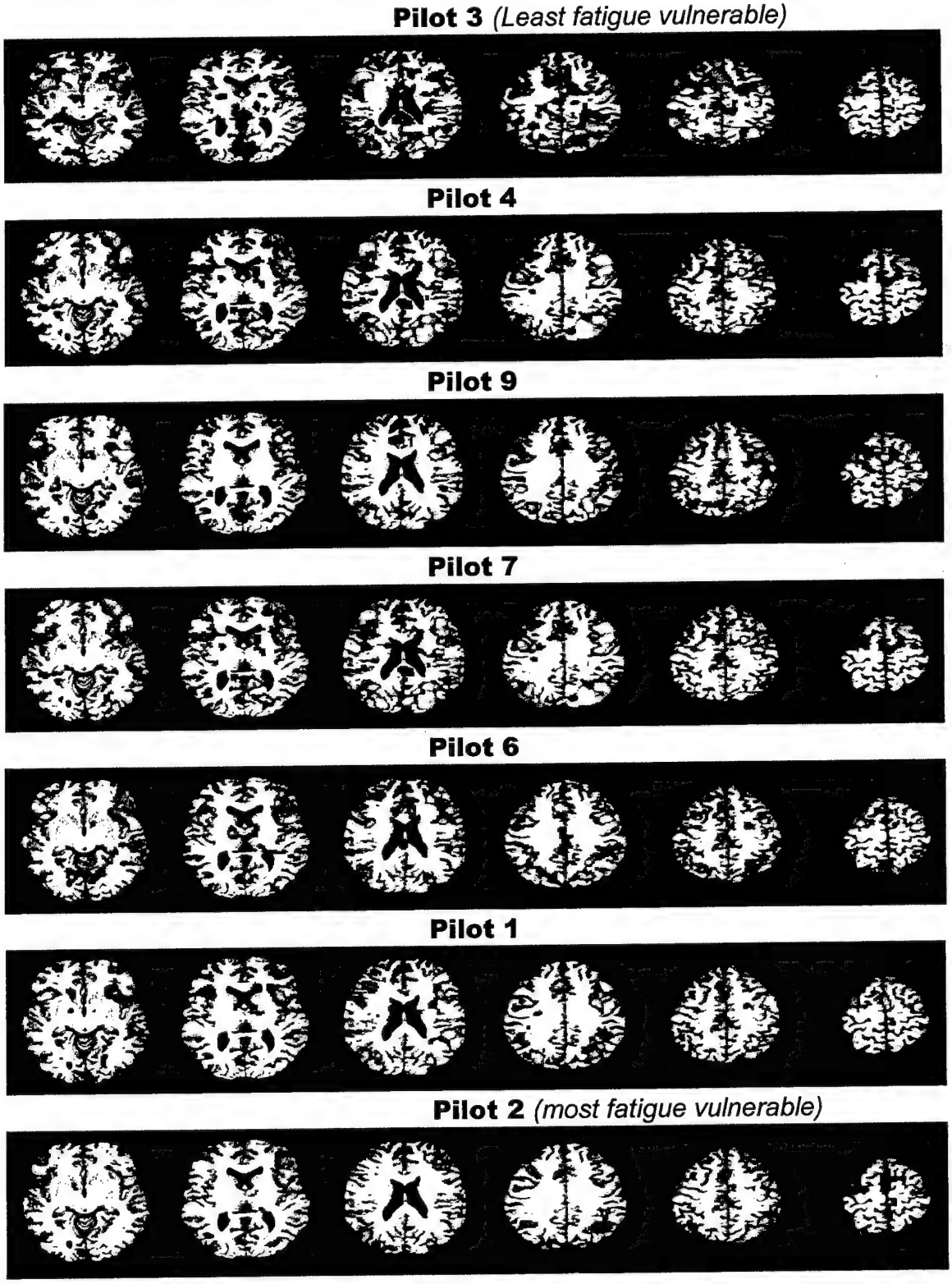

Figure 7. Individual pilots t-maps during performance of Sternberg Working Memory Test (SWMT) in the MRI scanner. (Maps were thresholded at $p < 0.05$ with a spatial extent $p < 0.05$, corrected for multiple comparisons.)

Correlations with maximum flight-performance deviations

The bivariate correlations between maximum flight-performance deviations and global and regional activation in response to SWMT were similar to those observed between average flight-performance deviations and the global and regional activation data (Table 2). Note that reasonably strong positive correlations were found between the flight data and the fMRI data in every case except of the left prefrontal region.

Table 2. Correlations between flight performance and fMRI results

Number Activated Voxels	Average Flight Performance	Maximum Flight Performance Deviation
Global	0.849	0.762
Left Prefrontal	0.446	0.309
Left Parietal	0.727	0.731
Right Prefrontal	0.872	0.790
Right Parietal	0.899	0.889

Relationship between flight performance and other variables

Once it was found that fatigue susceptibility in flight performance could evidently be predicted by baseline fMRI data, other potential relationships were examined in an attempt to rule out several obvious confounds. In this analysis, age, flight experience, amount of sleep prior to performance testing (recorded via actigraphy), amount of self-reported sleep prior to fMRI scanning, and self-reported habitual sleep were correlated both with the average flight performance and the maximum flight-performance deviation. As shown in Table 3, none of these variables correlated significantly with the performance of interest.

Table 3. Correlations between flight performance and potentially confounding variables

Variable	Average Flight Performance	Maximum Flight Performance Deviation
Age	-0.028	-0.114
Total Flight Experience	-0.159	-0.341
Flight Experience in F-117	-0.377	-0.501
Sleep before fatigue study	0.469	0.538
Self-reported sleep before fMRI	-0.471	-0.553
Self-reported habitual sleep	0.179	0.204

DISCUSSION

The present investigation reiterated the earlier findings of Caldwell et al. (2003) that there are significant fatigue-related decrements in the simulator flight performance of experienced pilots who are kept awake for 37 continuous hours. Noticeable accuracy losses became especially apparent after 26-27 hours without sleep and continued throughout the remainder of the sleep-deprivation period. At these times, average group performance declined approximately 45 percent below well-rested levels. Such findings are consistent with previous reports demonstrating that fatigue impairs a variety of skilled performance as well as vigilance, alertness, and mood (Dinges, 1995).

In addition, the present research confirmed the existence of marked individual differences in fatigue vulnerability similar to those reported by Wilkinson (1974), Morgan et al., (1980), and Van Dongen, Rogers, Dinges (2003). One of the 10 pilots described in the present research was virtually unaffected by sleep deprivation, whereas others suffered average performance decrements ranging from 11 to 60 percent and peak performance degradations ranging from 25 to 135 percent.

However, despite this level of individual variability, there was evidence from the fMRI scans that as a group, the present sample of F-117 pilots tended to be more physiologically fatigue resistant than another recently-evaluated sample of volunteers. The pilot fMRI data revealed baseline patterns of cortical activation that were more similar to those of the fatigue-resistant non-pilots tested earlier by Mu et al. (in press) than to those of the fatigue-vulnerable non-pilots tested in this earlier study. In fact baseline scans indicated the pilots and the fatigue-resistant non-pilots were characterized by an average of 6,870 activated voxels and 4,545 activated voxels respectively, whereas the fatigue-vulnerable non-pilots had only 1,584 activated voxels during performance of

the SWMT. Even the pilots with the lowest performance had at least twice the number of activated voxels than the average fatigue-vulnerable non-pilot. Thus, as a group, the pilots appeared to be quite fatigue resistant, assuming that an increase in baseline cortical activation is related to an increase in fatigue tolerance as postulated by Mu et al. (in press). Whether this increased fatigue resistance was due to self-selection, Air Force selection procedures, or some sort of long-term adaptation to the fatigue of working extended periods (with minimal sleep) is unknown. A follow-on longitudinal study that tracks pilots from initial training to the end of their flight careers would help to address this issue.

Evidence that an association between fMRI patterns and fatigue tolerance may exist was offered by the series of within-group analyses used to correlate the pilots' flight data with their fMRI measures of global and regional activation. These analyses revealed statistically significant positive relationships between fatigue resistance (in terms of flight performance) and the amount of cortical activation in response to SWMT. This was the case for global activation ($r=.85$) as well as for right-prefrontal ($r=.87$) and right-parietal activation ($r=.90$). The relationship with left-parietal activation was marginally significant as well ($r=.73$). Thus, it appears that the greater the amount of baseline cortical activation, the less performance will be affected by fatigue during a period of sleep deprivation—further confirming the earlier hypothesis set forth by Mu et al. (in press). This relationship does not appear to be confounded by participant characteristics such as age, experience, pre-test sleep amounts, or habitual sleep needs, although the present small study does not obviate the need to examine these factors in a more systematic manner.

With regard to the predictive utility of the regional fMRI measures collected here, it was of interest to note that the level of cortical activation in both parietal regions seemed well-related to performance vulnerability, whereas only activation in the right prefrontal region (but not the left prefrontal region) appeared to offer important predictive information. Given earlier reports regarding the particular sensitivity of the prefrontal cortex to sleep deprivation (Drummond et al., 1999; Thomas et al., 2000), these results were somewhat surprising since it might have been suspected that this cortical region would have offered the most valuable information about fatigue vulnerability. Instead, the present findings appear more consistent with the observations of Mu et al. (submitted) that, at least when using a verbal memory task, the bilateral parietal cortex is particularly sensitive to sleep loss. This may be because this region is thought to mediate the short-term storage and retrieval of phonologically coded verbal material (Jonides et al., 1998; Smith and Jonides, 1998; Smith, Jonides, Marshuetz, and Koeppe 1998). It would be interesting to further explore the predictive utility of prefrontal activation versus parietal activation by implementing scans that included both arithmetic tests (such as those used by Drummond et al. and Thomas et al.) and verbal-memory tests (such as the SWMT used here). This should be an objective of future research.

SUMMARY AND CONCLUSIONS

The present study, in which active-duty military pilots were tested under conditions of sleep deprivation before later completing non-sleep-deprived fMRI scans, indicated: 1) that as a group, even well-trained aviators suffer serious degradations in basic piloting skills; 2) that some pilots are clearly more affected by sleep loss than others; 3) that despite the observed decrements in group performance, the pilots appeared to be less fatigue vulnerable than two previously-tested groups of non-pilots; and 4) that

non-sleep-deprived fMRI evaluations possess utility for predicting the degree to which specific individuals will be able to tolerate the fatigue from sleep deprivation. Further research is recommended to validate these findings in a larger sample of participants, to systematically explore the potentially-confounding effects of individual sleep needs, and to determine whether increased fatigue-resistance can be learned or otherwise developed. Also, it would be worthwhile to explore whether employing different types of cognitive tasks during the fMRI scanning procedure affects the predictive utility of these scans.

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